Synthesis of fused heterocyclic compounds containing pyrimidine /triazepine/ pyrazole rings and studies on their biological activities.

Introduction:

Heterocyclic compounds containing nitrogen, sulphur, and oxygen have been receiving much more attention during the recent years. The compounds Triazine, Triazole, Tetrazole, Oxazole, Imidazole, and pyrazole have reported to possess a wide range of biological activities. Some fused heterocyclic rings like pyrimidine pyrazole, benzothiazole, benzoxazole benzimidazole, pyrimido-triazipine have been also reported an effective pharmacophores. Such fused heterocyclic compounds with their important pharmacophores would exhibit better pharmacological activities.

The incorporation of an imidazole, thiazole, and oxazole nucleus, a biologically accepted pharmacophore likes Benzimidaozle, Benzothiazole and Benzoxazole respectively molecules have made it's a versatile heterocycles possessing a wide spectrum of biological activity. As these important heterocycles are associated with anticancer, antibacterial, antifungal, anti-inflammatory, analgesic activities, one may well expect the fused heterocyclic rings containing pyrimidne / pyrazole/ triazepine/ triazines to display potent biological activity against different parasite and physiological disorders.

In view of the reported biological activities of heterocycles containing pyrimidine / triazepine/ pyrazole rings, it is proposed to study the toxicity risk assessment, structure activity relationship which would help to design, synthesize the biologically active target molecules. Such fused heterocycles may contain Benzoxazole, Benzothiazole, Benziimdazole, Triaizpine, Pyrazole Tetrazole nucleus in target molecule.

Review of literature and Development in the subject (Previous work done in the relevant area):

A survey of literature reveals that heterocyclic compounds containing Benzoxazole, Benzothiazole and Benziimdzole fused with different pharmacohores like pyrimidine / triazine/ triazipine / pyrazole possess various biological activities.

Benzoxazole moieties have attracted special attention in chemistry and biochemistry. These heterocycles exhibit various pharmaceutical properties such as antiviral, antibiotic, antibacterial, antifungal, antitumour, antitutercular, anti-inflammatory and analgesic activities[1]. It has also been shown that 1 and 10-ethylated products of fused pyrimido benzimidazole reported as CNS depressant and anti-inflammatory cativities[2-3]. Hemal M Soni et al [4] have reported the novel antitubercular agents by combining pyrazoline and benzoxazole pharmacophores. P K Jahuri et al [5] synthesized 2-substituted benzooxazole and reported to possess anticancer activity. Sharad V Kuberkar et al [6] reported the one pot synthesis of substituted 1, 2, 4 triazipino benzothiazole possessing antibacterial activity.

Objectives of Research/Proposed Hypothesis:

The objectives of proposed research work are-

- To prepare substituted /unsubstituted 2-amino or hydrazino benzooxazole / Benzimidazole / Benzothiazole.
- To prepare reagents like Bis-methylthio methylene malononitrile, Ethyl-3-cyano bis-methylthio acrylate, and other reagents to get fused heterocycles .
- To prepare substituted 2-amino /hydrazine pyrimidine and fused pyrimido pyrimidine and its derivatives.
- To prepare triazipino / pyrazolo compounds fused with benzoxazole/ benzimidazole and their derivatives.
- To study the pharmacological activities of all synthesized compounds like, antimicrobial, anticancer and other activities etc.

Methodology to be adopted:

It is proposed for the synthesis of starting compounds like 2-amino/ hydrazino substituted benzoxazole / benzimidazole / benzothiazole and the required cyclizing reagents likes Bis- methylthio methylene malononitrile / 3-cyano bis-methylthio acrylate and other. Then the synthesis of fused heterocyclic compounds is to be carried out by using starting compounds with reagents to achieve the target molecule i.e fused pyrimido Benzoxazole / Benzimidazole / Benzothiazole by simple condensation reaction in presence anhydrous K_2CO_3.

Further synthesis of fused Triazipino and pyrazolo pyrimido Benzoxazole / Benzimidazole / Benzothiazole is to be carried out in presence of Na_2CO_3/K_2CO_3 by conventional method. Moreover their derivatives also prepared by using selected nucleophiles like substituted phenols / amines / sec. heteryl amines/ active methylene compounds, under the similar reaction condition. Finally the study of pharmacological screening of all the synthesized compounds would be reported, that would be beneficial for the society.

Importance of study / Society application:

It is very important to think about serious diseases like AIDS and Cancer diseases, because no any effective drugs are available in medicine to control the particular types of cancer. Many researchers are working on such interesting area to achieve positive result in medicinal chemistry, and as part of research contribution of our research group reported synthesis such fused heterocyclic compounds like fused pyrimido / triazipino / pyrazolo compounds with benzoxazole/ benzimidazole /benzothiazole. The resulting fused heterocycles would exhibit better antimicrobial, anticancer anti-inflammatory activities.

- **International status:**

Recent observation regarding the serious diseases like cancer, AIDS attract more attention to synthesize such drugs, they would be effectively active against the diseases. Many scientists all over the world are working on the same problem, like cancer. The drug contains benzoxazloe / Benzimidazole/ Benzothiazole moieties have proved to work as anticancer, antimicrobial activities from number of scientific journal in chemistry. Hence we thought to design and work on the synthesis of fused heterocycles and to study their expected biological activities.

- **National Status:**

Many researchers from the nation are working on the synthesis of heterocyclic compounds but our research group is highly interested to work on fused heterocyclic compounds expected to possess better pharmacological activity.

- **Significance of the study:**

Synthesized novel fused heterocyclic compounds would possess good Pharmacological/biological activities. The proposed heterocyclic fused heterocyclic compounds containing hetero atom like nitrogen, sulphur, oxygen are expected to exhibit antimicrobial, anticancer, anticonvulsant, anti-inflammatory activity. This proposed study would be expected beneficial for the human being.

Proposed work plan/ Formulation and structure of study:

The year wise plan of proposed research work is given as belows.

- **First year :**

- Reference work is to be carried on benzoxazole, benzimidazole, benzothiazole.
- Synthesis of substituted benzoxazole, benzimidazole, benzothiazole and their characterization.
- Synthesis of required reagent (Bis methylthio methylene malononitrile, and 3-cyano bis-methylthio acrylate)For cyclization to get fused compounds.

- **Second year :**

- Reference work on fused pyrimido benzoxazole /benzimidazole
- Synthesis and characterization of pyrimido benzoxazole /benzimidazole/ benzothiazole and it's derivatives.
- Submission of samples for the screening of pharmacological activities like antimicrobial/ anticancer,/ antitubercular and others etc.

- **Third year:**

- Synthesis of fused trazipino benzoxazole/benzimidazole/benzthiazole and it's derivatives
- Synthesis of fused pyrazolo benzoxazole/benzimidazole/benzthiazole and it's derivatives.
- Spectral characterization of all synthesized products.
- Biological evaluation of all newly synthesized compounds.

References:

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